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Chemical waves in cell and developmental biology

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Many biological events, such as the propagation of nerve impulses, the synchronized cell cycles of early embryogenesis, and collective cell migration, must be coordinated with remarkable speed across very large distances. Such rapid coordination cannot be achieved by simple diffusion of molecules alone and requires specialized mechanisms. Although active transport can provide a directed and efficient way to travel across subcellular structures, it cannot account for the most rapid examples of coordination found in biology. Rather, these appear to be driven by mechanisms involving traveling waves of chemical activities that are able to propagate information rapidly across biological or physical systems. Indeed, recent advances in our ability to probe the dynamics of signaling pathways are revealing many examples of coordination of cellular and developmental processes through traveling chemical waves. Here, we will review the theoretical principles underlying such waves; highlight recent literature on their role in different contexts, ranging from chemotaxis to development; and discuss open questions and future perspectives on the study of chemical waves as an essential feature of cell and tissue physiology.

Introduction

A fascinating question in biology is how spatiotemporal coordination is achieved in cells, tissues, and populations. There are many examples of this kind of organization in biological systems, ranging across scales, from synchronized cell divisions in early embryos (Clutterbuck, 1970; Foe and Alberts, 1983; Chang and Ferrell, 2013; Deneke et al., 2016) to coordinated cardiac contractions in the heart (Bers, 2002). For spatiotemporal coordination to arise, signals must spread through space and time. A fundamental mechanism by which molecules spread through space is simple diffusion, i.e., the random motion of molecules caused by thermal energy (Fig. 1 A). Diffusion tends to homogenize differences in concentrations of molecules and can operate very quickly on small spatial scales. For example, an average-sized protein would take only 2 s to diffuse 10 μm. However, as the distance increases, the diffusion time will increase as the square of the distance (Fig. 1 B). The same protein would take ~1.3 h to diffuse across an embryo that is 500 μm long. Thus, diffusion is too slow to coordinate biological events that occur across large distances within

seconds to minutes. Moreover, diffusion tends to dampen signals (Fig. 1 C), whereas spatiotemporal coordination of biological events often requires propagation of unperturbed signals, for example as traveling pulses.

One mechanism by which a signal can propagate quickly in a biological system without significant distortion is through active transport along actin filaments or microtubules (Fig. 1 D). For example, motor proteins, such as dyneins and kinesins, can bind to a large variety of signaling molecules and transport them at speeds of ~1 μm/s (Lomakin and Nadezhdina, 2010). Such motors mediate the shuttling of several cellular components, including organelles (Barlan et al., 2013) and the axonal transport of proteins toward the nerve terminals and back from nerve terminals to the neuron body (Millecamps and Julien, 2013). Other subcellular structures that have been proposed to provide directed motion of molecules are thin, long cellular structures such as cytonemes or nanotubes that can transport signaling molecules between distant cells (Buszczak et al., 2016; Kornberg, 2017). Unlike diffusion, active transport does not slow down with increasing distances (Fig. 1, E and F). In larger cells, the activity of molecular motors can generate fluid flows called cytoplasmic streaming, which can enhance transport and, under the appropriate physical conditions, also lead to increased diffusivity and enhancement of reactive fluxes (Goldstein and van de Meent, 2015; Quinlan, 2016).

The mechanisms described thus far pose two major limitations for achieving spatiotemporal coordination: they are either too slow and dampen signals, as is the case with diffusion alone, or they require specialized molecular motors and large, directional cellular structures such as long microtubule filaments, as in active transport. As a consequence, neither of these mechanisms are sufficient to explain all the remarkably rapid behaviors observed in biology. These limitations can be overcome by another mechanism that can spread a signal in space and time: traveling chemical waves. In chemical waves, biochemical activities diffuse over short distances and trigger rapid activation in neighboring regions via positive feedback (Winfree, 1972; Tyson and Keener, 1988; Gelens et al., 2014; Ishihara et al., 2014). The coupling of diffusion and positive feedback enables chemical waves to spread a signal rapidly and maintain their amplitude as they travel (Fig. 1, G–I). Classic examples of chemical waves in biology are the propagation of action potentials in neurons, and calcium waves after fertilization in early embryos and during heart contractions (Hodgkin and Huxley, 1952; Stricker, 1999; Bers, 2002). The

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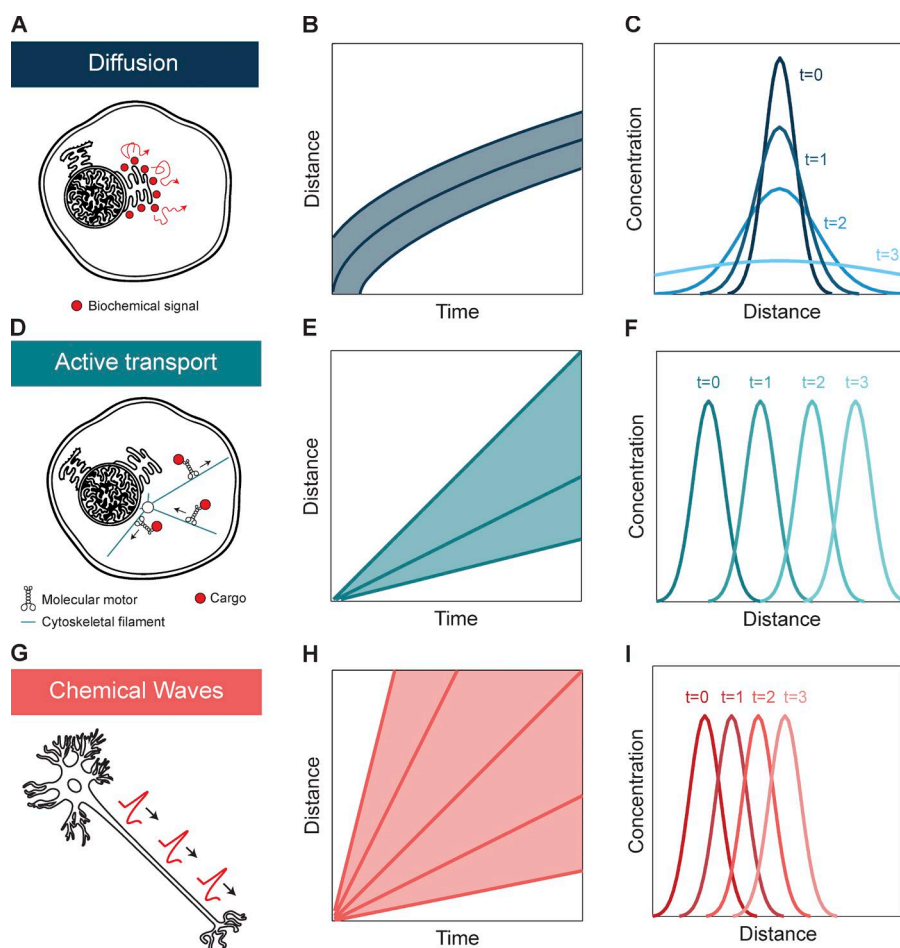
Figure 1. **Sending biochemical signals in cells.** **(A)** Schematic of a biochemical signal diffusing through a cell. **(B)** Distance traveled as a function of time by diffusion. Shaded regions represent relative range over which different-sized molecules diffuse. **(C)** Spreading of the concentration profile of a biochemical signal by diffusion. **(D)** Molecular motors can carry cargo through a cell by moving along cytoskeletal filaments in a process called active transport. **(E)** Distance traveled as a function of time by active transport. A narrower range of velocities (shaded area, E) has been observed for systems relying on active transport than for systems relying on chemical waves (shaded area, H). **(F)** Propagation of the concentration profile of a biochemical signal by active transport. **(G)** Chemical waves are the basis by which action potentials can rapidly spread signals through a neuron. Depicted is a traveling action potential. **(H)** Distance traveled as a function of time by chemical waves. **(I)** Propagation of the concentration profile of a biochemical signal by chemical waves. Diffusive transport dampens signal, whereas active transport and chemical waves preserve the amplitude of the traveling signal. Peaks are closer together in I compared with F to convey that chemical waves can travel much faster.

speed and range over which chemical waves operate highlights their potential to promote rapid communication. A list of the physical parameters that have been measured for numerous examples of chemical waves in biology is summarized in Table 1. Recent advances in imaging technologies and quantitative, interdisciplinary approaches have resulted in numerous new examples that further illustrate the importance of chemical waves as an essential means of communication in biological systems. In this review, we provide a conceptual and theoretical introduction to chemical waves, as well as recent examples detailing the role of chemical waves in embryogenesis, cell motility, and wound healing.

Theoretical framework of chemical waves

Biological systems have an inherently dynamic nature: molecules are constantly reacting and diffusing. This dynamic behavior is captured by reaction–diffusion equations, which can reproduce a wide range of processes, including traveling chemical waves and self-organizing patterns (Murray, 2002). Reaction–diffusion behaviors like self-patterning Turing systems (Turing, 1952), in which repeated patterns (e.g., stripes and spots) arise from the spatiotemporal interplay of activators and inhibitors in chemical pathways, have been reviewed elsewhere (Meinhardt, 1982; Kondo and Miura, 2010). Here, we focus on the distinction between active and passive waves and

Table 1. **Summary of physical parameters of key examples of chemical waves in biology**

System	Traveling activity	Estimated diffusion	Wave speed
		$\mu m^2/s$	$\mu m/s$
Xenopus extract cell cycle	Cdk1	10	1
Starfish and *Xenopus* cytokinesis	Rho	~0.03–1	~0.2
Drosophila syncytial cell cycles	Cdk1	5	2–6
Chemotaxis	Cdc42	~0.1–20	1
Actin waves	Hem1	~0.5	3–5
Wound healing	ERK	~1	~0.02
Growing epithelial culture	Mechanical stress	NA	~0.02
Somitogenesis	Notch signaling	NA	~0.02
Blood clotting	Thrombin	~85	~0.6
Eye imaginal disc	Dpp	~0.1–20	$\sim 10^{-3}$

NA, not applicable.

on the theoretical principles underlying the properties of different classes of waves.

Active and phase waves. In reaction–diffusion systems, diffusion generates mixing of molecules in space. Such mixing, when coupled to chemical reactions that rapidly amplify signals, can result in traveling waves of biochemical activities (Tyson and Keener, 1988; Gelens et al., 2014). Consider a large cell with inactivated proteins that are uniformly distributed. A pool of these proteins gets activated on one side of the cell through a phosphorylation event. For example, in the mitotic regulation of *Xenopus laevis* egg extracts, inactive cyclin-dependent kinase 1 (Cdk1) is believed to be first activated at the centrosome (Jackman et al., 2003; Ishihara et al., 2014), whereas in *Drosophila melanogaster* embryos, this activation happens at the poles (Foe and Alberts, 1983; Deneke et al., 2016). Activated Cdk1 can diffuse from the centrosome to neighboring regions. Furthermore, the reaction dynamics of Cdk1 is such that its activation leads to the catalytic activation of neighboring inactive Cdk1 through positive feedback (Morgan, 2007). The combination of local diffusion and the amplifying signaling network can lead to a traveling wave of activation of Cdk1 throughout the extract or embryo (Novak and Tyson, 1993; Chang and Ferrell, 2013; Ishihara et al., 2014; Deneke et al., 2016). Waves of this nature are considered active waves, and the central questions when studying such waves are identifying the molecules involved and dissecting the reaction kinetics necessary to drive the initiation and propagation of chemical waves.

Wave-like patterns do not necessarily indicate that there is a traveling chemical wave. For example, it is possible for a field of cells to be "prepatterned" in such a way that individual cells will trigger some biochemical activity at a time determined by some internal timer. The internal timers could be set such that cells at one end of the field trigger first, and then their neighbors trigger a little later, and so on, until cells at the other end of the field trigger last. A sensor for the biochemical activity would detect that activity apparently propagating from one end of the field to the other, in a manner indistinguishable from a traveling wave. Such apparent waves are called phase waves or kinematic waves but are based on a preexisting pattern of timer settings rather than a propagating signal as in traveling waves (Winfree, 2001). Such waves have been proposed as mechanisms to explain waves of gene expression in somitogenesis (see Waves of gene expression in the formation of somites), the anaphase wave following the active mitotic entry wave in *Drosophila* embryos (see the Mitotic waves section), and embryonic patterning of the short-germ beetle *Tribolium castaneum* by the Caudal morphogen gradient (El-Sherif et al., 2014). The difference between active waves and phase waves is the first fundamental question that needs to be addressed when determining the mechanisms of wave-like spreading in biological contexts. The mechanisms can be distinguished by introducing a physical (diffusion) barrier within the system. Active waves cannot proceed past a barrier, so the two physically uncoupled compartments would become uncoordinated (Fig. 2 A). In contrast, if a phase wave is prepatterned by the delays introduced by a previous chemical activity, then the wave-like propagation would be unperturbed by the presence of the diffusion barrier (Fig. 2 B).

Mathematical types of waves: unstable, bistable, and excitable. Chemical waves can have many types of reaction dynamics, and these determine the physical properties of the wave. They fall under three major mathematical classes: unstable wave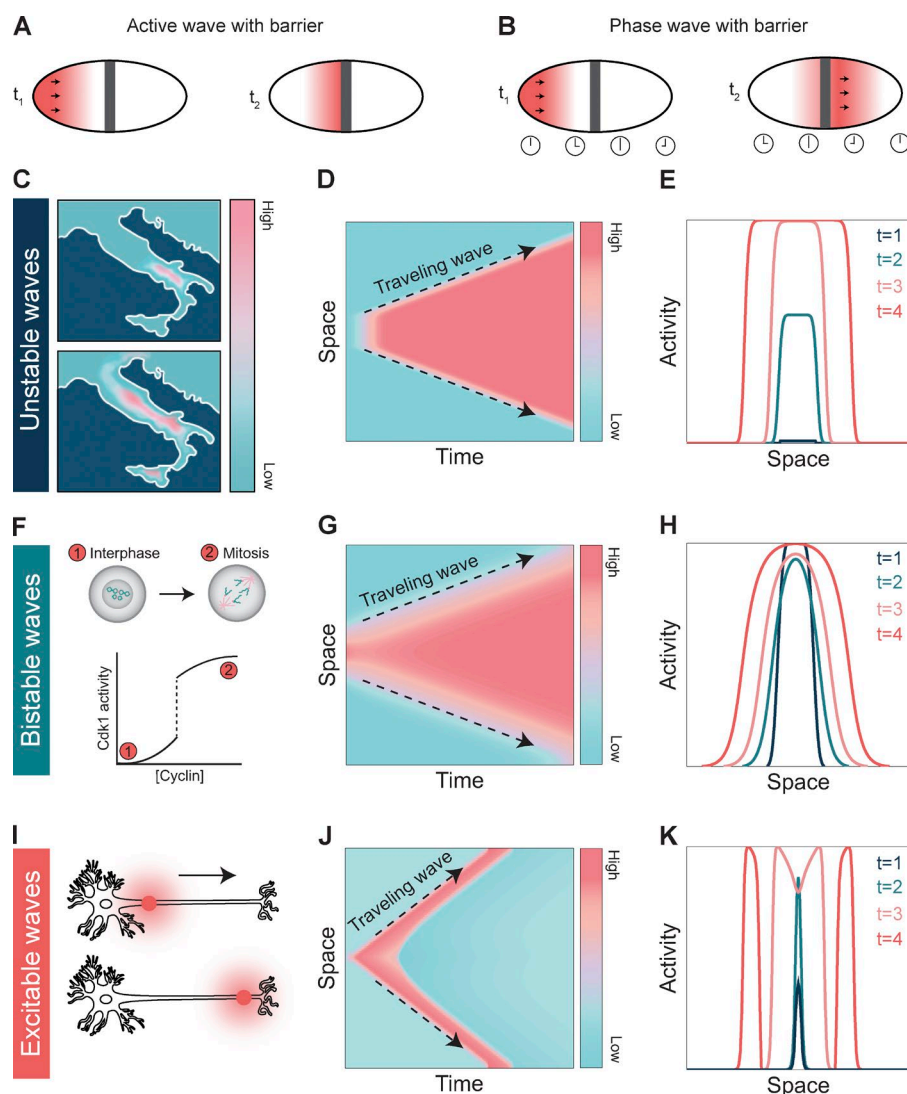s, bistable waves, and excitable waves (Murray, 2002; van Saarloos, 2003). These three wave types can be distinguished mathematically by analyzing the concentration dynamics of a key regulator in the system (see text box).

Unstable waves arise in systems that are initially in a state where any small fluctuation will shift them toward a more stable state. These unstable systems can be intuitively understood by models of population growth. In these models, a population will first grow exponentially when few individuals are present and eventually will slow down and reach its carrying capacity. Mathematically, the population dynamics can be described by a logistic growth equation that produces an S-shaped curve. The most notable example of unstable waves are Fisher–Kolmogorov waves, which were first used by Fisher in 1937 to describe the spatial spreading of an advantageous allele through a population (Fisher, 1937; Kolmogorov, 1991). Advantageous alleles can diffuse to neighboring regions, start growing exponentially in these regions, and thereby spread in a wave-like pattern (Fig. 2, D and E). Fisher–Kolmogorov waves have found wide applications in population genetics and social studies, where they have been used to describe gene drives, the spreading of farming throughout Europe (Fig. 2 C), and migratory waves of people in the United States (Ammerman and Cavalli-Sforza, 1971; Baggaley et al., 2012; Tanaka et al., 2017). Nonetheless, the importance of unstable waves in cell and developmental biology remains unclear. In principle, unstable waves would be very sensitive to noise, which can easily drive a system away from the unstable point and randomly initiate wave propagation. A possible way by which cellular pathways could use unstable waves more accurately is by the regulated activation of a pathway that causes a stable state to become unstable, thereby achieving control of the spreading of an unstable wave.

Bistable and excitable waves have so far been more widely observed in cellular and developmental systems. A bistable system is characterized by two stable states, e.g., a low and high state of activity. In biological systems, bistability usually arises from nonlinear positive feedback (Ferrell and Ha, 2014). For concentration values between the two stable states, the concentration will either increase or decrease. A threshold exists such that values below the threshold evolve to the low steady state and values above the threshold evolve to the high steady state. As soon as the transition from low to high state is triggered in a given region, activity can diffuse to neighboring regions, shifting these regions above the activation threshold and therefore causing the transition from low to high. The new activity in this region can then itself propagate and initiate the transition in the next region, and so on, effectively generating a traveling wave (Fig. 2, G and H). In physics, a typical example of traveling waves observed in a bistable medium are the waves driving solidification in supercooled liquids (van Saarloos, 1998), where solid and liquid phases represent the two stable states. The cell cycle control network is a canonical biological example of a bistable system, with interphase and mitotic Cdk activity represent the two states (Fig. 2 F; Morgan, 2007).

Much theoretical work has been developed to understand the properties of waves spreading in bistable media (van Saarloos, 1998). Most of the work in the physical literature has focused on bistable systems in which the parameters that characterize bistability are not time dependent (van Saarloos, 1998). For supercooled liquids, experiments are conducted by slowly cooling the liquid and then very rapidly perturbing it to induce solidification, so that the wave propagates at a fixed temperature. However, this assumption is not always justified

A Active wave with barrier

B Phase wave with barrier

C Unstable waves

D

E

F Bistable waves

G

H

I Excitable waves

J

K

Figure 2. **Theoretical mechanisms of chemical waves.** **(A and B)** Introduction of a physical barrier in a tissue/embryo allows the distinction between an active (A) and a phase wave (B). **(C)** Wave-like spreading of farming through Italy, adapted from Baggaley et al. (2012). **(D and E)** Propagation of Fisher–Kolmogorov unstable waves spreading through space. **(F)** Diagram representing bistable regulation of the cell cycle transition from interphase to mitosis. Cdk1 activity exhibits a switch-like/bistable response as a function of cyclin concentration. **(G and H)** Propagation of bistable chemical waves. **(I)** Diagram representing the spreading of an action potential through an axon in a neuron. **(J and K)** Excitable wave spreading through space and time.

for biological systems, which tend to display bistability only transiently, for example in transitions that are controlled by the accumulation of proteins. Our theoretical understanding of chemical waves spreading through transiently bistable media remains limited, and it is likely that new mechanisms of wave-like spreading will emerge in biological systems that are driven rapidly out of equilibrium.

An excitable medium is a system that has only one stable state but two modes of returning to that state, which are established by nonlinear feedback dynamics (Strogatz, 2000b; Murray, 2002). Positive feedback operates to generate a threshold-like response, and negative feedback acts to reset the system to steady state. One prominent example of an excitable system in biology is the neuron. Neurons are normally at a resting potential. As a neuron is stimulated, its potential changes until it reaches a threshold. At this point, the neuron emits a spike, i.e., a large electrical signal, before relaxing back to its resting potential. The spike is then able to rapidly travel down the axon as a wave (Fig. 2 I), through a mechanism that emerges from the coupling of diffusion and excitability (Murray, 2002). Excitable waves are characterized by constant speed, constant wave amplitude, and a threshold for activation. In cell and developmental contexts, genetic networks characterized by positive and negative feedback can, under the appropriate conditions,

generate an excitable system (Lindner et al., 2004; Süel et al., 2006). In neurons, an increase in the membrane potential leads to the opening of ion channels, which results in a further rise in the membrane potential. This positive feedback drives the system past the threshold in neighboring areas. Once the membrane potential is at its peak, ion channels rapidly inactivate and another set of ion channels open to reset the initially "excited" region back to equilibrium. The net effect of these dynamics is a pulse of high activity traveling as a wave (Fig. 2, J and K; Murray, 2002). Similarly, the aggregation of individual *Dictyostelium discoideum* amoebae is driven by traveling excitable waves of cAMP (Alcantara and Monk, 1974; Siegert and Weijer, 1995; Gregor et al., 2010; Kamino et al., 2011).

Measuring chemical waves in biological systems. Experimentally, the analysis of chemical waves, arising in reaction–diffusion systems, requires the ability to measure both the reaction and diffusion processes independently. Several optical methods have been developed for measuring the diffusion of molecules in biological tissues (Lippincott-Schwartz et al., 2001; Miyawaki, 2011). Measuring the reaction processes could be experimentally more difficult, depending on the nature of the molecular mechanisms that control the reactions that generate waves. For systems in which the waves arise from feedbacks in signaling dynamics, optical techniques to measure the

Mathematical basis for classes of waves
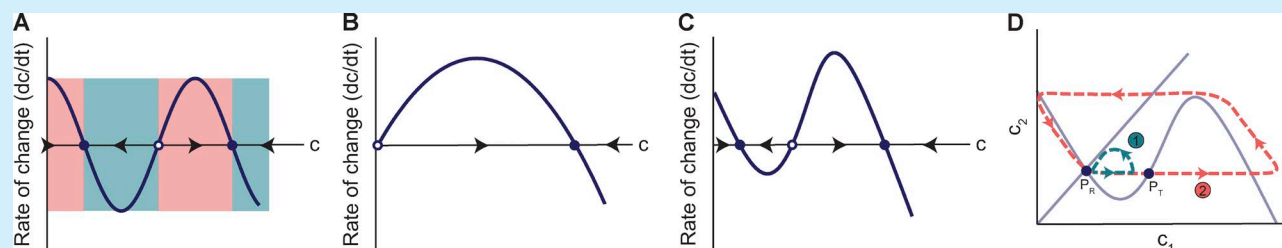
The behavior of dynamical systems characterized by a single differential equation can be understood using a graphical approach, known as phase plane analysis (Strogatz, 2000b). In this analysis, the rate of change of the concentration of a protein (dc/dt) is plotted as a function of the concentration itself (c). If the rate of change is positive, the concentration will increase—in other words, move toward the right in the phase plot (A, pink shaded). Conversely, if the rate of change is negative, the concentration will decrease, moving to the left (A, teal shaded). When the rate of change is zero, the system is at steady state, and this concentration is termed a "fixed point" (A, closed and open circles). Stable fixed points attract the system to converge toward them (A, closed circles), and unstable fixed points force the system to move away from the fixed point (A, open circles).

From this analysis, three mathematical types of waves arise. Unstable waves originate in reaction–diffusion systems in which the reaction dynamic is characterized by an unstable and a stable fixed point (B). Bistable waves, on the other hand, arise in systems that are characterized by two stable fixed points and an unstable fixed point in between them that serves as a threshold to transition from one stable point to the other (C). Finally, excitable waves take place in a system that has only one stable state but two modes of returning to that state, which are established by nonlinear feedback dynamics (Strogatz, 2000b; Murray, 2002). The phase plane for an excitable system cannot be described using a one-dimensional system. A system consisting of two variables (c_1 and c_2) is necessary to recapitulate the dynamics of excitable waves. Typical phase trajectories are depicted as dotted lines in D. An excitable system is initially at resting potential (P_R). A small perturbation that does not exceed the threshold potential (P_T) will result in the system returning to the resting potential (D, teal dashed line, loop 1). In contrast, if the perturbation is larger than the threshold, then the system will undergo a large excursion (D, pink dashed line, loop 2).

Mathematical relations can be derived for all three wave types. In an unstable wave, for example, the speed is $v = 2\sqrt{D\alpha}$, where D is the diffusion coefficient and α is the prefactor in the logistic equation (or for different unstable dynamics, the derivative of the reaction term at the unstable point). This relation for the speed wave, which could also be obtained by dimensional analysis, is named Luther's formula (Luther, 1906; Tyson and Keener, 1988) and is often generalized to other chemical waves. However, extending Luther's formula to other classes of waves (e.g., bistable and excitable waves) is not straightforward and requires careful mathematical analysis to identify the relevant timescale for the propagation of the wave (van Saarloos, 1998, 2003).

activity of biological molecules are required. The recent development of biosensors for several of the central pathways in cell and developmental systems makes it possible to analyze their dynamics quantitatively and with high spatiotemporal resolution (Regot et al., 2014). The combination of these techniques with theoretical models will allow us to test the importance of chemical waves as a mechanism for spatiotemporal coordination in different contexts (Bement et al., 2015; Deneke et al., 2016). Here we highlight recent work in which chemical waves have emerged as a central feature of biological regulation at cellular and multicellular scales.

Bistable and excitable waves in the regulation of the cell cycle, cytokinesis, and cell motility

Mitotic waves. Chemical waves have ideal properties for systems that require very rapid propagation of a signal across a large distance. One common example is found in developing eggs that are laid externally, such as those of insects, amphibians, and fish. Despite their large size (0.5–1.2 mm), these eggs execute the fastest cell cycles observed in biology (~8–25 min/cycle; Graham and Morgan, 1966; Foe and Alberts, 1983; Kane and Kimmel, 1993; Kimmel et al., 1995). Even more remarkably, cell divisions in these eggs are coordinated with one another in synchronized "mitotic waves" (Hara, 1971; Foe and Alberts, 1983; Shinagawa et al., 1989; Rankin and Kirschner, 1997; Ogura and Sasakura, 2017). This global synchrony is important to ensure the proper execution of morphogenesis later in development.

The idea that the coupling of bistability and diffusion in the regulation of Cdk1, the main driver of mitosis, could generate traveling chemical waves that would account for the observed mitotic waves was first proposed theoretically by Novak and Tyson (1993). More recently, in vitro experiments using a

Xenopus extract system confirmed that chemical waves of activity synchronize the cell cycles (Chang and Ferrell, 2013). When *Xenopus* egg cytoplasm was combined with nuclear-targeted GFP and chromatin in a Teflon tube, waves of nuclear envelope breakdown and reformation were observed to propagate at a constant speed of ~1 µm/s (Fig. 3, A and B). Importantly, when the tube was bisected, the nuclei on one half became uncoupled from the nuclei on the other half, suggesting that an active wave coupling mechanism which requires local diffusion was in place (Fig. 3 C). The mitotic waves in *Xenopus* were proposed to arise from a bistable system centered on Cdk1 and its regulation by two positive feedback loops involving Wee1 and Cdc25 during M phase. To determine whether this mechanism occurred in vivo, Chang and Ferrell (2013) measured the speed of surface contraction waves, a downstream cytoskeletal effect of Cdk1, in fertilized eggs. Indeed, the speed of these waves matched the speed observed in the cycling extracts and followed the spatiotemporal dynamics predicted by an active wave mechanism (Chang and Ferrell, 2013).

Further insights into these contraction waves and their relation to cytokinesis in both frog and starfish embryos was obtained via the demonstration that coordinated waves of Rho activity and F-actin assembly generate an excitable cortex that can orchestrate cytokinesis (Fig. 3 D; Bement et al., 2015). The Rho-actin waves propagate at speeds of ~0.2 µm/s and have a fixed time delay, with F-actin waves following Rho activity waves (Fig. 3, E and F). Mathematical modeling suggests that waves arise in a reaction–diffusion system, in which Rho acts an activator and F-actin as an inhibitor (Bement et al., 2015). The model displays a weak global excitability early on, which progresses to a strong localized excitability at the equator. This local excitability is thought to enable the cortex to rapidly adapt to signals from dynamic spindle orientation, suggesting that excitable chemical waves play a role in the spatial coordination of
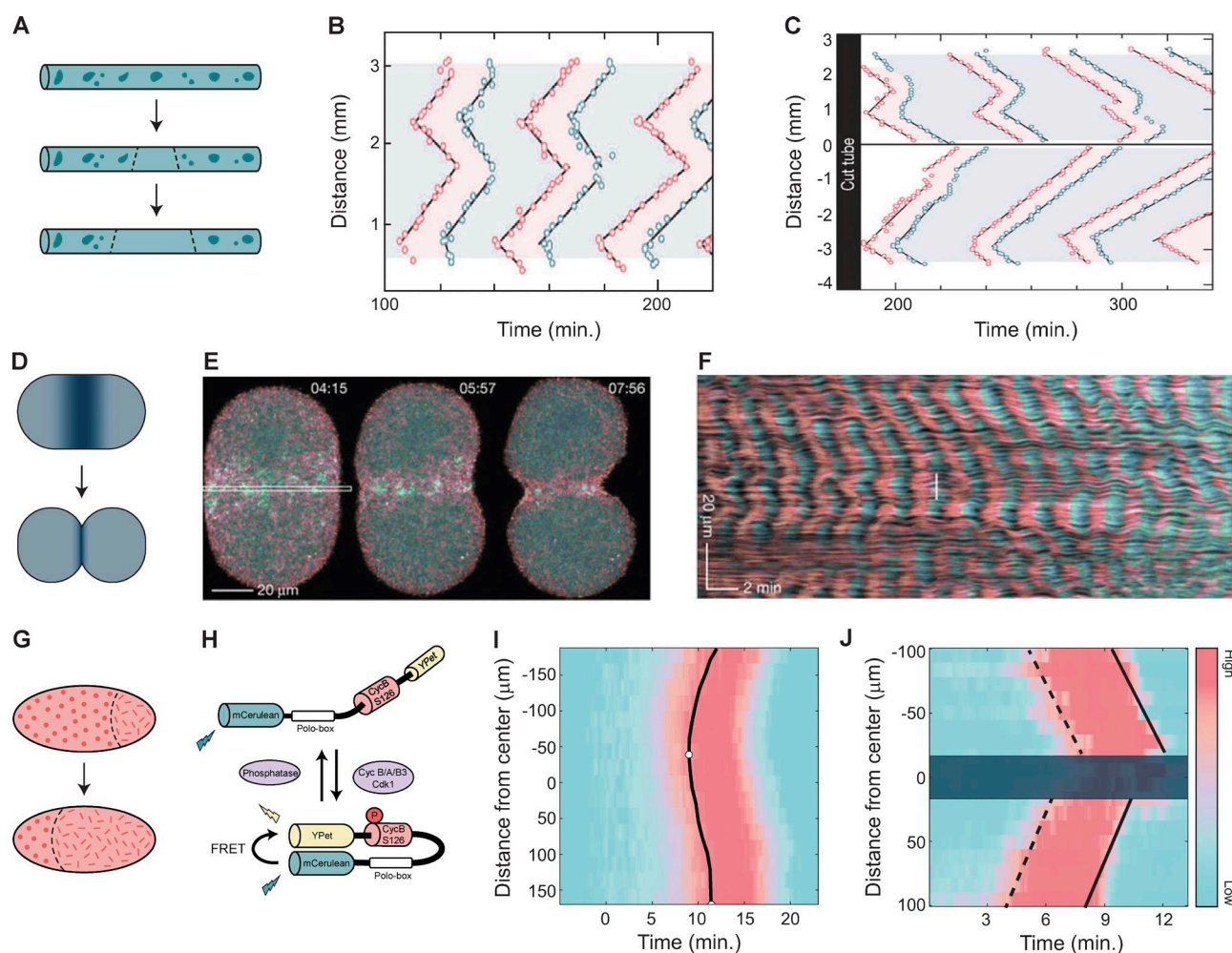
Figure 3. **Examples of bistable and excitable chemical waves in biology.** (A) Schematic of mitotic waves in *Xenopus* egg extracts. Teal blobs represent interphase assemblies of sperm chromatin and nuclear-targeted GFP in a Teflon tube. Upon mitotic entry, blobs disassemble in a wave-like fashion. (B) Waves of mitotic entry (pink circles) and exit (blue circles) in *Xenopus* egg extracts. Adapted from Chang and Ferrell (2013). (C) Uncoupled mitotic waves upon physical separation of the extract in two halves. Adapted from Chang and Ferrell (2013). (D) Schematic of cytokinetic ring formation. (E) Starfish embryo coexpressing GFP–rGBD (cyan; Rho activity) and GFP-Utr (pink; F-actin) undergoing cytokinesis. Adapted from Bement et al. (2015). (F) Kymograph of an activated frog egg overexpressing Ect-2 depicting Rho-activity (cyan) and actin (pink) waves. Adapted from Bement et al. (2015). (G) Schematic of mitotic waves in a developing *Drosophila* embryo. (H) Schematic of Cdk1 FRET sensor: active Cdk1 complex induces a conformational change that increases FRET efficiency. (I) Heatmap of Cdk1 wave in a cell cycle 13 *Drosophila* embryo. Black line, mitotic entry wavefront; white circles, wave origins. (J) Uncoupled Cdk1 waves after the introduction of a barrier during S phase. Dotted line, mitotic entry front; solid line, mitotic exit front; shaded region, barrier. Adapted from Deneke et al. (2016).

cytokinesis. Rho and F-actin excitability are modulated by Cdk1 activity, thus providing a link to cell cycle dynamics (Bement et al., 2015). This coupling might arise from a traveling wave of Cdk1 activity in frog embryos (Chang and Ferrell, 2013) and a gradient of Cdk1 activity in starfish embryos (Bischof et al., 2017). In cultured adherent cells, mitotic cortical waves of Cdc42 activity and of the F-BAR protein FBP17 might provide both positional and size information to specify the cell division plane (Xiao et al., 2017), suggesting a role for chemical waves in cell size control. It has been speculated that linear waves in reaction–diffusion systems represent a strategy for size control in biological systems (Laughlin, 2015).

The experiments just described provide evidence for chemical waves in the long-range spatial coordination of the first cell cycle of frog embryos. Importantly, these mechanisms might only apply to the first cell cycle of *Xenopus* embryos, when the cell is very large and positive feedback plays an important role in the regulation of the cell cycle. Application of

a steep temperature gradient across a frog egg allows the desynchronization of cell division, suggesting that cells are not spatially coupled and behave as independent oscillators (Anderson et al., 2017). Therefore, in *Xenopus* embryos, long-range spatial coordination takes place only during the first cell cycle and not in later stages, when cells become small and are separated by membranes and positive feedback is less important (Tsai et al., 2014).

The role of chemical waves in the synchronization of embryonic cleavage cycles and the mechanistic dissection of these waves can be addressed in the syncytial *Drosophila* embryo, a multinucleated cell with a shared cytoplasm, which is amenable to sophisticated live-imaging approaches. The *Drosophila* embryo develops as a syncytium for the first 2 h of development, during which it divides 13 times in a synchronized fashion (Fig. 3 G; Rabinowitz, 1941; Foe and Alberts, 1983; Farrell and O'Farrell, 2014; Ferree et al., 2016). It was recently shown that chemical waves of Cdk1 activity synchronize the cell cycles

(Deneke et al., 2016). Using a fluorescence resonance energy transfer (FRET) biosensor of Cdk1 activity (Gavet and Pines, 2010a,b), Cdk1 waves were visualized directly for the first time (Fig. 3 H). Waves were found to propagate at speeds of ~2–6 µm/s (Fig. 3 I). The wave speed progressively slowed down as the embryo approached the maternal-to-zygotic transition (Idema et al., 2013; Deneke et al., 2016), which corresponds to a switch from rapid cell cycles, driven by maternal products and independent of transcription, to patterned cell cycle events (Farrell and O'Farrell, 2014; Ferree et al., 2016). It is intuitive to assume that the speed of the wave would be controlled by the rate of Cdk1 activity during mitotic entry. However, in *Drosophila* embryos, the activity of Cdk1 during mitosis was found to be invariant throughout development and could therefore not account for the observed slowdown of the wave speed. Surprisingly, changes in the rate of Cdk1 activation during S-phase do account for the physical properties of the waves. The importance of S-phase regulation of Cdk1 waves was demonstrated by introducing a barrier between two regions of the embryo during S or M phase. When the barrier was introduced during interphase, the two sides became asynchronous (Fig. 3 J), but when the barrier was introduced at the onset of mitosis, the wave of anaphase traveled unperturbed. This observation implies that Cdk1 waves observed during S phase are active waves, which can be described by a bistable reaction–diffusion system (Deneke et al., 2016), whereas the mitotic waves are kinematic waves that follow after a fixed delay. This demonstrated a fundamental distinction between the mitotic waves in *Xenopus*, which were proposed to be coupled during M phase, and the Cdk1 waves in *Drosophila*, which were shown to be coupled during S phase. A similar phenomenon in which an apparent mitotic wave is controlled by a wave-like pattern during S phase has been observed during neurulation of ascidian *Ciona intestinalis* embryos, demonstrating an interesting parallel strategy for the generation of a mitotic wave across an embryo (Ogura and Sasakura, 2016). Interestingly, both the M phase and S phase waves arise in the context of bistable regulation of Cdk1, suggesting that dissecting the control of mitotic waves requires careful analysis of possible mechanisms of regulation of bistable waves. These waves allow efficient synchronization and provide temporal accuracy by reducing the variability and noise sensitivity intrinsic to bistable systems (Balázsi et al., 2011).

Chemotaxis, cell migration, and mechanical waves. Another interesting system in which wave-like patterns have been observed is steering cells during chemotaxis, where a locally excitable Cdc42 signal precedes cell turning and hence serves as a local compass to direct the cell to migrate toward the chemoattractant (Yang et al., 2016). In this study, the authors investigated the migration dynamics of neutrophil-like cells in response to a gradient of chemically caged chemoattractant that was released upon ultraviolet illumination (Collins et al., 2015). They found that Cdc42 is steeply polarized at the leading edge of chemotaxing cells and that this signal is wave-like and propagates at a speed of ~1.1 µm/s. The locally excitable Cdc42 signal, therefore, allows a cell to rapidly generate one or more protrusive fronts that can then become restricted to a single front through additional mechanisms. It remains to be elucidated whether the wave-like phenomena observed in this system serve a functional role or whether they are a by-product of the existence of positive and negative feedbacks. At a tissue level, waves could mediate the coupling of neighboring cells to facilitate collective cell migration.

Similarly, actin traveling waves that arise through cycles of activation and inhibition of actin nucleation have emerged as major regulators of cell migration. One of the first examples of actin waves was in human neutrophils (Weiner et al., 2007). The dynamics of a key regulator of actin nucleation, Hem-1, showed cycles of activation and inhibition that generated propagating actin waves. Since then, actin waves have been observed and proposed as a fundamental feature of cell migration in many systems such as fibroblasts, *Dictyostelium*, and keratocytes (Vicker and Grutsch, 2008; Machacek et al., 2009; Allard and Mogilner, 2013; Barnhart et al., 2017; Devreotes et al., 2017; Inagaki and Katsuno, 2017). More recently, it was shown that in fish keratocytes, local excitable dynamics of actin polymerization led to protrusions at the leading edge (Barnhart et al., 2017). Given the small size of these cells, it is not intuitive that the role of the waves in this system is to propagate a signal faster than diffusion. However, waves can enhance the ability of a cell to steer by propagating signals that are locally amplified. The development of quantitative models will be crucial to dissect the molecular mechanisms of the waves and extend these insights to complex geometries such as 3D systems.

An important role for chemical waves has also emerged in the coordination of collective cell migration during wound healing. For example, the existence of calcium waves driving cytoskeletal reorganization in this context has long been recognized (Benink and Bement, 2005; Xu and Chisholm, 2011; Cordeiro and Jacinto, 2013). Such is the case in the *Drosophila* notum, where a wave of actomyosin apical constriction that is associated with a calcium wave is observed in response to injury (Antunes et al., 2013). Traveling waves of extracellular signal-related kinase (ERK) signaling have been proposed to play a role in collective cell migration after wound healing (Hiratsuka et al., 2015). First observed during skin renewal in mice (Hiratsuka et al., 2015), these waves travel outwards from the injury site and may arise from a mechanism similar to the one just described for bistable waves. An in vitro model can recapitulate features of the in vivo system, arguing that actomyosin contractility and collective cell migration are regulated by the ERK signaling wave, so that cells migrate in the opposite direction of the wave (Aoki et al., 2017). Remarkably, induction of an ERK signaling wave using an optogenetic tool results in collective migration in the direction opposite to the wave (Aoki et al., 2017).

Wave-like cellular reorganization and patterning of tissues could also be generated by mechanical signals. In epithelial tissues, adhesive forces are able to propagate mechanical stresses across cells, and wave-like propagations of mechanical stresses have been observed in the expansion of epithelial monolayers (Serra-Picamal et al., 2012). Cytoskeletal reinforcement and relaxation of the stresses are required to generate these waves, which travel at a very slow speed and are, therefore, likely to play a role in coordinating tissue growth on long timescales.

Chemical waves in other developmental and physiological contexts

The chemical waves described here in the regulation of the cell cycle, cytokinesis, and cell motility can be dissected theoretically through the analysis of bistable and excitable reaction–diffusion systems (Fig. 2). The function of these waves is to transfer information rapidly across tissues or cells (Fig. 1). In this section, we briefly discuss chemical waves that might originate from different theoretical models and display a wider range
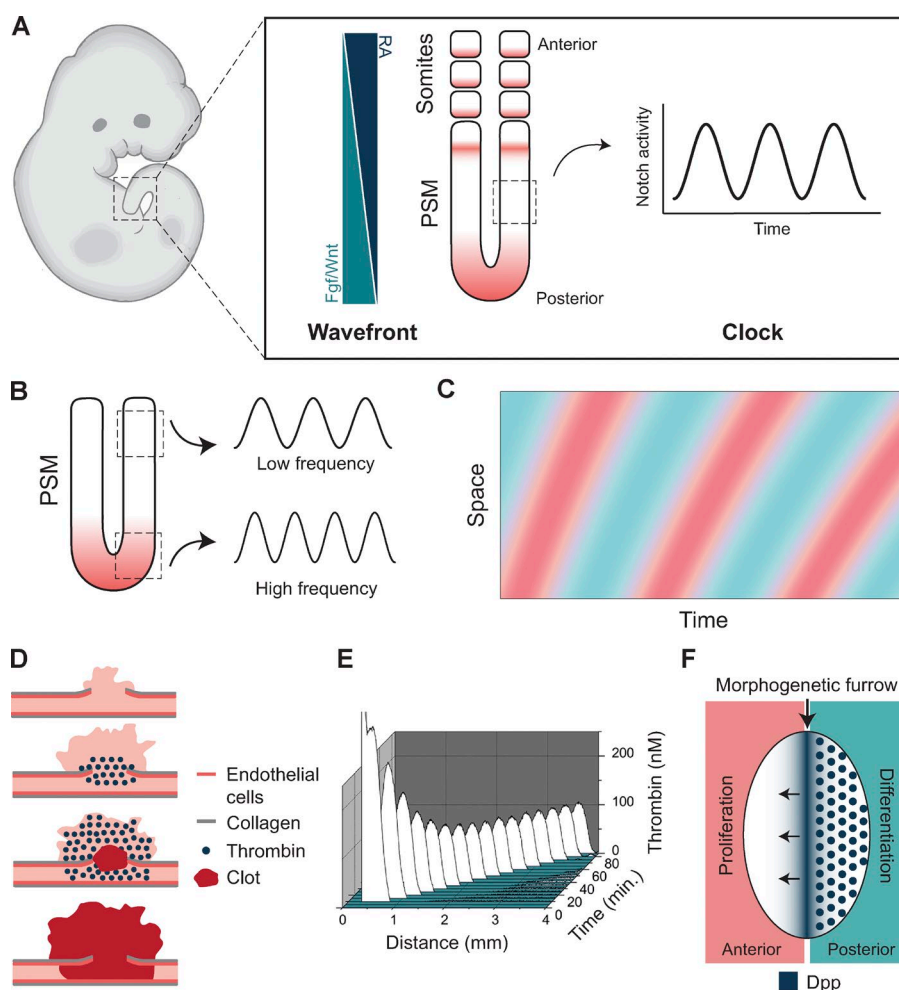
Figure 4. **Additional examples of chemical waves in biological systems. (A)** Schematic of clock-wavefront model for somitogenesis. The PSM exhibits oscillatory gene expression that generates waves that sweep from posterior to anterior. **(B)** Schematic of PSM showing how gene expression oscillations have different frequencies along the anterior-posterior axis. **(C)** Heat map showing waves generated by a gradient of frequency through space. **(D)** Schematic of clot formation upon injury. Upon contact with collagen layer (gray), thrombin (navy circles) gets recruited to the site of injury and spreads in a wave-like manner. The thrombin wave is followed by a delayed antagonistic wave that results in the formation of a localized blood clot (red). **(E)** Spatiotemporal distribution of thrombin activity wave. Adapted from Dashkevich et al. (2012). **(F)** Schematic of a *Drosophila* eye imaginal disc, showing a morphogenetic furrow moving from posterior to anterior and organizing cell differentiation and cell proliferation.

of timescales, suggesting that chemical waves have roles in the regulation of multicellular organization that extend beyond the rapid transfer of information.

Waves of gene expression in the formation of somites. In vertebrates, somites are specified in the presomitic mesoderm (PSM) in a recurring, sequential manner, resulting in a segmented pattern (Oates et al., 2012; Hubaud and Pourquié, 2014). The prevailing model for somite formation is the clock-wavefront model (Fig. 4 A; Cooke and Zeeman, 1976; Hubaud and Pourquié, 2014). In this model, formation of somites requires two major components: a cell autonomous oscillator (the clock) and a wavefront, which represents a wave of maturation across the PSM set by dynamical signaling gradients of proteins or small molecules (Fgf, Wnt, RA, etc.). Once the clock meets the wavefront in the right conditions (phase of the clock and levels of the gradients forming the wavefront), cells differentiate into somites. During this process, waves of gene expression span from the posterior to anterior of the PSM and lead to the specification of a somite at the anterior side (Masamizu et al., 2006; Aulehla et al., 2008). The traveling waves are generated by both a frequency and a phase gradient along the anterior-posterior axis (Gomez et al., 2008; Oates et al., 2012; Lauschke et al., 2013; Soroldoni et al., 2014; Shimojo and Kageyama, 2016). This is illustrated in Fig. 4 (B and C), where the signaling activity of cells, oscillating in a frequency gradient, is plotted as a function of space and time and gives rise to a wave pattern (Fig. 4 C).

To determine whether the observed waves of gene expression were active or kinematic, Maroto et al. (2005) dissected the PSM into small fragments and found that they maintained their synchronized oscillations compared with the intact control, an observation consistent with kinematic waves. However, when individual cells were dissociated from the posterior side of the PSM and cultured in vitro, they oscillated asynchronously (Maroto et al., 2005), indicating an important role for cell–cell contact/communication (Oates et al., 2012). Synchronization of the segmentation clock depends on Notch signaling, which is essential for the coherent spatiotemporal wave pattern (Jiang et al., 2000). The importance of this cell–cell coupling was demonstrated by experiments in which individual cells from the PSM are isolated and randomly mixed together (Tsiairis and Aulehla, 2016). After a few hours, cells begin to display synchronized oscillations of a Notch signaling reporter, and traveling waves of gene expression emerge. Mixing cells from different regions of the PSM or isolated at different stages of oscillation indicated clearly that cells are able to adjust their frequency and phase in response to their neighbors.

Theoretically, the waves observed in these experiments are reminiscent of waves observed in systems of coupled oscillators. These systems have been extensively studied in mathematics. Kuramoto's model, for example, describes the dynamics of a large number of oscillators that can influence each other's phase (Kuramoto, 1984; Strogatz, 2000a). This coupling among oscillators pushes them toward a similar phase; if it is

sufficiently strong, it can synchronize them and, under certain conditions, generate traveling waves (Rodrigues et al., 2016). Several experimental and theoretical analyses based on these ideas have revealed significant insights on the process of somitogenesis (Riedel-Kruse et al., 2007; Lauschke et al., 2013; Soroldoni et al., 2014). However, this model of phase-coupled oscillators has recently been brought into question, as it was proposed that the waves of somitogenesis might, in fact, arise from an excitable system (Hubaud et al., 2017). In cultures reconstituted from isolated PSM cells, oscillations are initiated in both a density-dependent and substrate-dependent manner, suggesting a role for mechanical and cytoskeletal cues. This idea was strengthened by experiments demonstrating that signaling from the Yap pathway, which is known to be important in mechanotransduction (Panciera et al., 2017), affects the ability of PSM cultures to undergo collective, synchronized oscillations, that spread as traveling waves (Hubaud et al., 2017). Analysis of a mathematical model of excitability (FitzHugh–Nagumo model) demonstrated that several experimental observations are compatible with the behaviors of an excitable system involving both Notch and Yap signaling pathways (Hubaud et al., 2017). We expect that further quantitative imaging experiments and theoretical analyses will reveal the mechanisms regulating the properties of the waves, thus shedding light on a fundamental developmental process.

Waves in blood coagulation. Another example of an active wave phenomenon has been proposed in the process of blood coagulation. An advantage of having a wave-like response in wound healing is the ability to coagulate quickly across distances of millimeters to centimeters. Upon vascular injury, blood is released and comes into contact with a layer of collagen, which is present in the layer of extracellular matrix surrounding the vessels (Ataullakhanov et al., 1998). This contact promotes the release of thrombin, an enzyme that drives the process of blood clotting (Fig. 4 D). Using an in vitro model of wound healing, traveling waves of thrombin activity were observed by measuring the cleaving event of a fluorogenic thrombin-specific peptide substrate (Fig. 4 E; Dashkevich et al., 2012). These thrombin activity waves exhibited the canonical features of an excitable wave: constant speed, constant wave amplitude, and a threshold for activation. A potential problem that arises from triggering a wave of coagulation is restricting the wave to the wound site. In response to this issue, a second antagonistic wave that stops the spreading of the coagulation wave has been proposed for clotting to be locally confined (Ataullakhanov et al., 1998). These observations have been limited to in vitro studies; therefore, the role of thrombin activity waves in more complex tissues such as the adult skin in the context of wound repair remains to be elucidated.

Waves in patterning cell cycle and cell differentiation in *Drosophila*. A well-characterized system that displays a moving signaling wavefront is the *Drosophila* eye imaginal disc. In this system, Dpp and Hedgehog, a set of interacting signaling pathways, specify a morphogenetic furrow that travels across the tissue from the posterior to the anterior as a function of time (Fig. 4 F; Roignant and Treisman, 2009). The major function of this moving furrow is to organize the pattern of cell differentiation and cell proliferation in space and time (Baker, 2007). The movement of the furrow is driven by an autocatalytic regulatory loop involving the Hedgehog morphogen (Roignant and Treisman, 2009). Cells that receive the Hedgehog ligand differentiate. As they differentiate, they express and

release the Hedgehog ligand themselves, thus inducing the neighboring anterior cells to differentiate and release the ligand. This generates a traveling wave (Roignant and Treisman, 2009). The moving morphogenetic furrow clearly does not transfer information rapidly, because it takes ~2 d for the furrow to travel over the 100–200 µm of the tissue, i.e., a speed approximately four or five orders of magnitude smaller than the speed observed in the mitotic waves of early embryogenesis (Roignant and Treisman, 2009). We speculate that a traveling wave in this developmental context provides a sharp spatial separation between the region of proliferation and that of differentiation. For such separation to be effective, the timescale of the moving wavefront must match the intrinsic timescales of proliferation and differentiation, which are on the order of hours, not seconds or minutes. This is achieved by introducing a delay of ~1–2 h in the feedback loop, regulating Hedgehog expression (Roignant and Treisman, 2009). Specifically, Hedgehog activates the release of the epithelial growth factor ligand, Spitz. Spitz is received by neighboring cells, which in response activate the Punt transcription factor, which is responsible for transcription of the *hedgehog* gene, thus closing the feedback loop (Roignant and Treisman, 2009). The delays imposed by transcription, translation of several factors, and processing of extracellular signals set the speed of the morphogenetic furrow. We propose that "slow" chemical waves in this system generate a sharp transition that allows for the precise control of transcriptional programs resulting in specific cell fate behaviors.

Perspective: Chemical waves as a general strategy to organize cellular dynamics in space and time

The multiplicity of biological processes described in this review suggests that chemical waves are ubiquitous in living systems. Their role in spreading biological signals rapidly across a large range of spatial and temporal scales is well established, as is the case in the coordination of embryonic cleavage divisions (Chang and Ferrell, 2013; Bement et al., 2015; Deneke et al., 2016). Conversely, the role of chemical waves in the coordination of cellular dynamics in larger and more complex tissues remain largely unexplored. More specifically, the mechanisms by which cellular transitions are coordinated in space and time and whether collective coordination of processes, such as cell proliferation, is required for normal development remain unclear. Cellular processes in complex tissues are often coordinated by the dynamics of signaling pathways, which are well described by reaction–diffusion models (Murray, 2002). Because waves are commonly observed in this class of mathematical models, it is very likely that more examples of chemical waves will emerge. Recent advancements in imaging methodologies (e.g., intravital imaging; Weissleder and Nahrendorf, 2015) and the development of molecular biosensors for several signaling pathways (Regot et al., 2014) will allow us to identify waves in a wider range of cellular and developmental processes. A wavefront traveling with little distortion and at constant speed provides sharp and accurate spatiotemporal responses to dynamical signals. These properties might be highly desirable in tissues in which cell differentiation and growth are tightly coupled, as discussed for somitogenesis and eye imaginal disc development.

It will also be fundamental to dissect whether these waves of signaling will emerge as a key mechanism of regulation of tissue morphogenesis and dynamics or arise simply as a byproduct of the feedback mechanisms required to regulate biological

dynamics. In some biological contexts, waves arising from the combination of diffusion and nonlinear dynamics could pose problems by generating unwanted signals that propagate through tissues (e.g., the fibrillation waves observed during heart contractions; Pandit and Jalife, 2013), and biological systems might have evolved mechanisms to suppress them. In this review, we have mainly focused on the ability of reaction–diffusion systems to generate sharp wavefronts. However, in two and three dimensions, waves of more complex geometries, for example spirals, can arise, and such waves of cAMP signaling have been observed during aggregation of the slime mold (Alcantara and Monk, 1974; Siegert and Weijer, 1995). Noise also can influence the properties of waves. For example, in a bistable system, noise could affect the transition time from the low to the high state and, in principle, initiate unwanted waves. These noise-driven events could be suppressed by precise temporal regulation, so that the initiation of the wave is controlled by an additional input, such as cyclin synthesis in the mitotic waves. The effect of noise on time-dependent bistable waves remains unclear, whereas for time-independent systems it can be shown that bistable waves, but not unstable waves, are insensitive to noise (van Saarloos, 1998).

From a theoretical standpoint, biology has inspired the development of several reaction–diffusion models. In fact, the first well-understood example of a wave in a reaction–diffusion equation was elaborated by Fisher and Kolmogorov et al. to describe the spatiotemporal spread of an allele through a population (Fisher, 1937; Kolmogorov, 1991). Physicists have also been very interested in waves arising in reaction–diffusion systems (often known in physics as Ginzburg–Landau equations), as they capture the behavior of systems undergoing phase transitions (van Saarloos, 1998). For that reason, a great body of theoretical work has been developed and provides the foundation for modeling biological systems. However, physical and biological systems often display fundamentally different characteristics, e.g., biological systems tend to change rapidly with time and are often far from thermodynamic equilibrium. We therefore expect that the unique properties of biological systems and our unprecedented ability to measure signaling dynamics in living systems will inspire new theoretical work and reveal important new insights into both the physical and molecular mechanisms by which chemical waves can arise in biology.

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