laminaris neurons could follow stimulation frequencies into the high kilohertz range. They termed this AC response 'sound analogue potential' because it indeed resembled the waveform of the pure-tone stimuli played to the owl's ears. Although such high-frequency responses had been postulated [15,16], this is the first experimental demonstration that nucleus laminaris neurons actually achieve them.

The second major finding of Funabiki *et al.* [1] is that although the amplitude of the sound-analogue potential was small (only 1–2 mV), it was this — and not DC-shifts of the membrane potential — that correlated linearly with the output spike rate. In other words, only the sound-analogue potential waxed and waned with varying interaural time difference and in turn drove the spiking response (Figure 1). A DC potential of comparable magnitude also developed during stimulation but remained invariant with interaural time difference and had no influence on spike rate. To thus discount any slow fluctuations in membrane potential is a huge deviation from ordinary neuron behaviour.

How Do The Cells Accomplish This?

Using a previously established neuronal model [15], Funabiki *et al.* [1] went on to explore the parameter space which would mimic most closely the *in vivo* responses. This distilled three conditions that appear especially critical at high best frequencies.

First, time constants of the synaptic input currents need to be shorter than anything previously measured in such neurons (for example, [17]). Funabiki *et al.* [1] predict a half-peak width of a unitary postsynaptic current of about 100 μs. This remains a challenge to explain biophysically.

Second, the cell body should not actively spike. A 'passive' soma with few or no voltage-activated Na^+ channels selectively enhances the interaural-time-difference sensitivity at high frequencies. This is basically related to the inactivation period of Na^+ channels that slows the membrane's time constant [15,18]. Furthermore, it is advantageous that the spike initiation site on the axon moves further away from the soma with increasing best frequency of the neuron [18] (Figure 1). Funabiki *et al.* [1] now add that a higher density of Na^+ channels at the axonal initiation site probably confers a crucial increase in sensitivity to the small sound-analogue potentials at high best frequencies.

Third, high spontaneous discharge rates of the inputs help to minimise the DC response of the membrane potential. Basically, a constant high-level input already in quiet depolarises the membrane by a steady amount and thus reduces any further depolarisation upon stimulation. This novel suggestion by Funabiki *et al.* [1] may explain the extraordinarily high spontaneous discharge rates of nucleus magnocellularis neurons which form the inputs to nucleus laminaris. These monaural input neurons discharge about 200 spikes per second in total quiet [19]! Several hundred of them typically converge on one nucleus laminaris neuron in barn owls [20], resulting in an impressive volley of synaptic events.

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DOI: 10.1016/j.cub.2011.12.023

Cell Polarization: Mechanical Switch for a Chemical Reaction

Anterior–posterior polarity in the *Caenorhabditis elegans* zygote depends on two groups of PAR proteins, as well as on cortical flow. Recent work now demonstrates that this polarization results from a transition in a bistable reaction–diffusion system of PAR proteins that is triggered by cortical flow.

Alexander B. Verkhovsky

How the cell acquires a direction is one of the most challenging and exciting problems in cell biology. Cell components may diffuse and interact with each other freely and randomly within the confines of the plasma

membrane, yet in polarized cells some components end up concentrating at one side, while others are confined to the opposite side. This sorting is essential, for example, when the cell migrates directionally or when the fertilized zygote divides asymmetrically to give rise to cell lineages forming different parts of the embryo. A recent paper in *Science* by Goehring *et al.* [1] sheds new light on how chemical and mechanical mechanisms act together to ensure fast and robust polarization in the *Caenorhabditis elegans* zygote. Similar principles could be at work in other systems, such as in migrating cells.

How are cell contents sorted during polarization? Numerous studies on specific structural and signaling components usually provide the following type of information: protein A localizes to a particular part of the cell because it is targeted there by protein B; localization of protein B, in turn, depends on protein C, etc. These findings may be important, but they explain neither how the asymmetry first appears, nor how it is maintained. The solution to these issues did not come from experimental biological studies, but from the visionary work of a mathematician. In a 1952 paper entitled 'The Chemical Basis of Morphogenesis' [2], the founder of computer science Alan Turing demonstrated that a system of two or more chemical reactions can spontaneously develop stable asymmetric spatial patterns from a nearly uniform state, provided that the reactions are linked through feedback loops (i.e., the reaction rate depends on the products of the same and/or other reactions) and the reactive substances have different diffusivities. As an example that can be comprehended at a qualitative level, one can imagine that a slowly diffusing (e.g., membrane-bound) compound auto-catalytically stimulates its own production from a fast-diffusing (e.g., cytoplasmic) compound, and at the same time inhibits a similar reaction for another pair of compounds. The slowly diffusing substances would then tend to segregate to different spatial domains. After Turing, reaction–diffusion mechanisms have been implicated in pattern formation in a wide variety of systems: examples include morphogen control over the development of multicellular organisms [3], regulation of the cytoskeleton and polarity in single eukaryotic cells by small GTPases [4], Min-protein-dependent selection of the cell-division plane in prokaryotes [5], and many others.

In the same seminal paper [2], Turing noted that mechanical factors, such as stresses, velocities and elastic properties of living matter, have to be taken into account together with chemical reactions and diffusion in order to understand pattern formation. This idea remains much less developed than that of pattern formation based purely on chemical reactions. One consequence of cellular mechanics is that reactive substances could be transported and mixed by molecular motors and/or cytoplasmic flows, which would influence the length scale of the emergent patterns [6], while in pure reaction–diffusion systems the length scale is set by diffusion. Additionally, movement of filaments by motor proteins could generate patterns independently of the reaction–diffusion mechanism [7,8]. The chemical reaction of ATP hydrolysis by motors is necessary in this case to provide energy, but is not involved in pattern formation in the same sense as in a reaction–diffusion system. Thus, the self-emergence of asymmetric cell organization could involve both chemical and mechanical mechanisms, but their relative contributions remain to be clarified.

In the new study, Goehring *et al.* [1] used a combination of experiments with mathematical modeling to elucidate how cell chemistry and mechanics generate polarity in a classical model system: the early *C. elegans* embryo. The anterior–posterior axis of the *C. elegans* zygote is defined by conserved PAR (partitioning-defective) proteins, the counterparts of which also have functions in cell polarity in many other systems [9,10]. Two groups of PARs — anterior and posterior PARs — associate with the membrane of the embryo in a mutually exclusive manner, presumably thanks to reciprocal inhibition of membrane binding by kinases associated with the competing PARs [10,11]. Prior to fertilization, anterior PARs localize uniformly to the membrane, while posterior PARs are in the cytoplasm. Fertilization is believed to induce local weakening of the cell cortex, resulting in cortical flow away from the fertilization site, i.e., towards the prospective anterior pole. Anterior PARs are apparently removed by the flow from the posterior pole, while posterior PARs start to associate with the cortex and eventually cover approximately half of the embryo. Then the cortical flow stops, but the polarized PAR domains persist.

Goehring *et al.* [1] generated a mathematical model of these events based on relatively simple assumptions. First, they considered that cortical flow transports PARs along the surface of the cell. PARs were presumed to be carried passively by the cortical flux (in contrast to another recent model [12] that assumed specific interaction of PARs with cortical contractile elements). The efficiency of such transport depends on the ratio of diffusivity of the carried particle to the flow rate. Simulations showed that observed flow rates are sufficient to effectively remove PARs from the posterior pole.

Next, the authors described competitive binding of PARs to the membrane with a reaction–diffusion formalism similar to the one developed for another system: Rho-family GTPases [4]. In this model, non-linear antagonistic feedback in membrane-binding reactions leads to bistability: the membrane tends to exist in either one of the two states, with only anterior PARs or only posterior PARs bound to it. Polarization is then equivalent to a transition from a uniform anterior-like state to a state with two segregated domains in opposite states. How does this transition happen in the cell? Theoretically, a random disturbance of sufficient amplitude could elicit the change, but in a cell this could result in improper geometry or timing of the transition. In contrast, cortical flow may be a physiologically relevant trigger. Simulations indeed showed that removal of the anterior PARs from the posterior pole by cortical flow was sufficient for binding of posterior PARs and subsequent rapid polarization.

Goehring *et al.* [1] further explored what would happen if either the mechanical or chemical component of the polarization mechanism were disrupted. The model predicted that, in the absence of flow, PARs could still polarize through the reaction–diffusion mechanism, but this would take a much longer time than with the flow. On the other hand, if the bistability of the

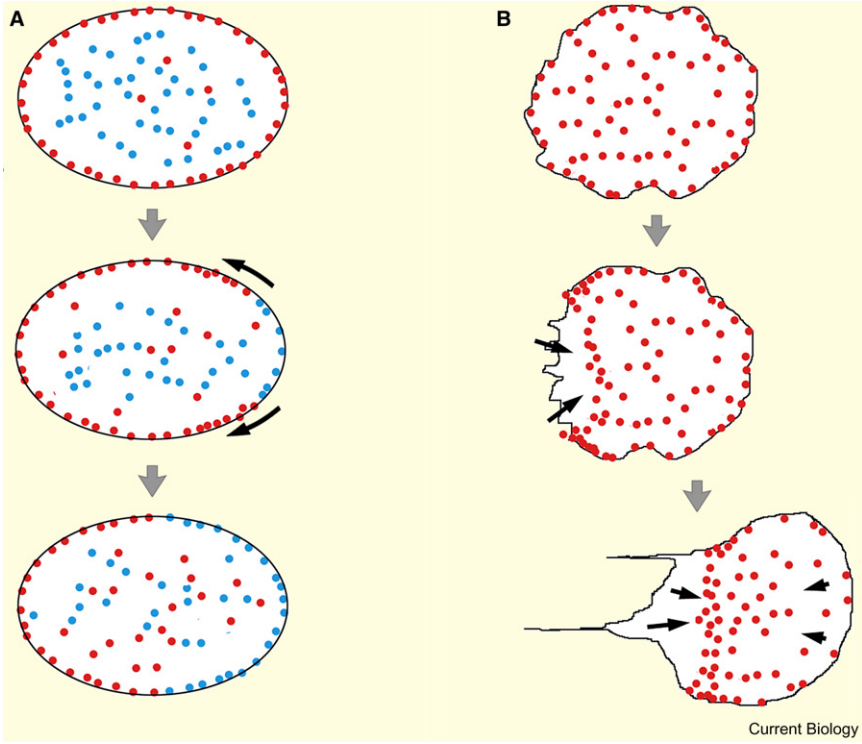

Figure 1. Cortical flow in cell polarization.

(A) In the *C. elegans* zygote, cortical flow displaces anterior PARs (red circles) from the posterior pole, thus allowing posterior PARs (cyan circles) to bind. This accelerates the eventual establishment of stable polarity through a reaction–diffusion mechanism. (B) In polarizing motile cells, local contraction at the prospective rear may similarly displace and/or concentrate a signaling molecule (e.g., a member of Rho-GTPase family), possibly reinforcing emerging polarity. Cortical flow persists in fully polarized migrating cells; thus, eventual distribution of the signaling molecule would depend on both flow pattern and the reaction–diffusion chemistry. (N.B. This cartoon is an illustration only and not intended to represent exact distribution.)

chemical reaction was not there (for example, in the absence of competing posterior PARs), the anterior PARs would still segregate under the action of flow, but only for as long as the flow persisted. Both of these predictions were in exact accordance with experimental data. The model also correctly described the exact shape, dynamics and steady-state position of the anterior–posterior boundary under several experimental perturbations. These findings demonstrate that polarization in the *C. elegans* embryo results from a coupling of cortical flow, which acts like a switch, to a bistable chemical reaction–diffusion system (Figure 1A).

What is next? Note that the current model does not consider the origin of cortical flow, nor any possible feedback from the PAR system to the flow [13]. Considering reciprocal interactions between reaction–diffusion chemistry and flow would be an interesting extension.

Could similar principles operate in other polarization events? There are numerous indications of the interaction between the cytoskeleton and PAR proteins in systems other than *C. elegans* [10], raising the possibility that cytoskeletal activities could couple to reaction–diffusion networks in such PAR-dependent processes as development of epithelial and neuronal polarity. In addition, contraction and actin flows are believed to play the role of a trigger in a class of polarization events that are not usually considered to be dependent on PAR proteins: the transition of migrating cells from a symmetric stationary state to directional motion. Local retraction elicited by a transient external force can set cytoplasmic fragments into motion [14]. Spontaneous initiation of polarization in fish epidermal keratocytes [15] and fibroblasts [16] is associated with increased contraction and actin retrograde flow at the prospective rear of the cell. It was proposed that actin flow concentrates myosin motors to the retracting rear of the cell, which, in turn, would reinforce the flow, thus maintaining polarization [14].

Is there a connection with the reaction–diffusion mechanism? Some of the effectors of Rho GTPases that control the actin network were reported to interact with PAR proteins [10,17]. Perhaps more importantly, Rho GTPases themselves were implicated in the generation of polarized patterns by means of a reaction–diffusion mechanism, thanks to feedback loops in their activation and differences in diffusivity between the membrane-bound and cytoplasmic forms [4]. Experimentally, the activity of Rho GTPases is distributed in a polarized manner [18], or oscillates in correlation with the cell edge dynamics [19] in migrating cells. Actin-dependent transport of the Rho-family GTPase Cdc42 was implicated in polarization in budding yeast [20]. It remains a challenge for the future to test whether cytoskeletal flows transport Rho GTPases or other signaling molecules to switch reaction–diffusion networks and elicit polarization of migrating cells (Figure 1B).

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DOI: 10.1016/j.cub.2011.12.012

Sexual Signaling: Climatic Carry-Over

A long term study of warblers in the Himalayas reveals a surprising contrast in the effects of warm springs as opposed to warm summers on a signaling trait, emphasizing the need to consider year-round influences of the environment on morphological variation.

Maren N. Vitousek*, Roi Dor, and Rebecca J. Safran

Sexual signals are widely used to convey information about their bearer to potential mates or competitors [1]. These signals are often condition-dependent, providing information about an individual's ability to withstand environmental challenges [2]. Current climate influences both condition and signal development, but until recently, little was known about whether signals reflected their bearer's ability to cope with prior environmental challenges [3,4]. Carry-over events — which occur in one season but influence success during subsequent seasons — have been demonstrated in a variety of species [5] and could have major influences on reproductive success in a rapidly changing climate. For example, when more of the non-breeding habitat of grey whales is covered by ice, females are in lower condition during the following breeding season, and produce fewer calves [6]. Such carry-over effects could be particularly influential for organisms that undertake large migrations and experience different environmental contexts along the way [7,8]. Examples include migratory songbirds whose plumage-based signals are typically developed in a non-breeding context, often months before their use during territory acquisition and mate selection.

Several recent studies [3,4] using long-term data sets have begun to reveal links between prior environmental conditions and signal traits, with populations showing increased signal expression in years when non-breeding environmental conditions were favorable. In male barn swallows of the European subspecies (*Hirundo rustica rustica*), for instance, the length of sexually-selected tail streamers is increasing over time in association with climate-driven resource availability during migratory stop-overs [9]. As many aspects of the environment are expected to change rapidly in the near future, it will be increasingly important to understand potential interactions between multiple climate variables and signal traits. In a recent issue of *Current Biology,* Scordato *et al.* [10] use data collected over a 25 year period to show that warmer than average temperatures during different periods have opposing effects on the subsequent expression of a sexual signal — wing bar size – in the Hume's warbler (*Phylloscopus humei*).

Male Hume's warblers (Figure 1) with larger wing bars reproduce earlier, and males manipulated to display larger wing bars increase their territory size, suggesting that this trait plays a role in male–male competitions during the breeding season [11]. The size of wing bars during the breeding season is determined by both the size of the trait during development, which occurs at the end of the breeding season and before long-distance migration, and the amount of wear during the non-breeding season. The surprising finding of Scordato *et al.* [10] is that the effect of increased temperature on wing bar size depends on the time during which temperature is elevated. When springs were warm, birds bred earlier, and early breeding was associated with the display of larger wing bars during the following breeding season. However, warm temperatures during the summer molt increased wear in the demelanized wing-bars. More worn bars had a smaller total bar area, suggesting that wing bar sizes were smaller in the breeding season following warmer summers. While spring and summer temperatures were not significantly correlated during the years of study, temperatures during both periods are increasing over time. Thus, an overall increase in breeding season temperatures due to climate shifts is expected to have contrasting influences on the size of the wing bar, a sexually selected trait.

Signaling in a Changing Climate

As global climate shifts, breeding dates are rapidly advancing in many bird species, driven by increasing spring temperatures [12]. Within populations, birds that arrive in better condition usually breed earlier, and early breeding itself confers a benefit to the individuals that are able to do so [13].